Infant Antiretroviral Prophylaxis (Updated September 14, 2011)

Panel's Recommendations

- The 6-week neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed neonates to reduce perinatal transmission of HIV **(AI)**.
- Zidovudine should be initiated as close to the time of birth as possible, preferably within 6–12 hours of delivery **(AII)**.
- The 6-week zidovudine prophylaxis regimen is recommended at gestational age-appropriate doses; zidovudine should be dosed differently for premature infants less than 35 weeks than for infants at least 35 weeks of age (see Zidovudine Dosing and Table 8) **(AII)**.
- In the United States, the use of antiretroviral (ARV) drugs other than zidovudine cannot be recommended in premature infants because of lack of dosing and safety data **(BIII)**.
- The use of intrapartum/neonatal zidovudine is recommended regardless of maternal history of zidovudine resistance **(BIII)**.
- Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen, begun as soon after birth as possible **(AI)**. A randomized, controlled trial has shown that a 2-drug regimen of zidovudine given for 6 weeks combined with three doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) is as effective as but less toxic than a 3-drug regimen of zidovudine, nelfinavir and lamivudine. The 2-drug regimen is preferred due to lower toxicity and because nelfinavir powder is no longer available in the United States (see General Considerations for Choice of Infant Prophylaxis and Table 9) **(AI)**.
- In other scenarios, the decision to combine other drugs with the 6-week zidovudine regimen should be made in consultation with a pediatric HIV specialist, preferably before delivery, and should be accompanied by counseling of the mother on the potential risks and benefits of this approach **(BIII)**.
- The National Perinatal HIV Hotline (1-888-448-8765) provides free clinical consultation on all aspects of perinatal HIV, including infant care.

Zidovudine Dosing

All HIV-exposed infants should receive postpartum ARV drugs to reduce perinatal transmission of HIV. The 6-week neonatal zidovudine chemoprophylaxis regimen is recommended for all HIV-exposed infants[1-2]. Table 8 shows zidovudine dosing intrapartum, which is a continuous intravenous infusion during labor, and neonatal dosing. Table 9 shows intrapartum and neonatal dosing for other drugs to be considered in certain situations as delineated below.

The recommended dose of zidovudine for post-exposure prophylaxis in full-term neonates is 4 mg/kg body weight orally twice daily for the first 6 weeks of life, beginning as soon after birth as possible and preferably within 6–12 hours of delivery (Table 8). Although the ACTG 076 study used a zidovudine regimen of 2 mg/kg every 6 hours, data from many international studies support twice-daily oral infant dosing for prophylaxis[3-12]. Most of these studies used a dose of 4 mg/kg twice daily, adjusted for weight gain, but others have used a regimen based on birth weight for the entire 6-week treatment period[13-14]. The current World Health Organization (WHO) guidelines recommend a simplified zidovudine dosing regimen for the 6-week prophylaxis period consisting of 10 mg given twice daily for infants weighing less than 2.5 kg at birth and 15 mg twice daily for infants weighing more than 2.5 kg at birth[15]. The advantages of this simplified regimen are that it avoids the need for dosing calculations and involves administration of either 1.0 or 1.5 mL of zidovudine syrup. The disadvantage is that, compared with mg-per-kg dosing, infants with birth weights greater than 3.75 kg will receive a smaller zidovudine dose and infants less than 3.75 kg will receive a larger zidovudine dose.

Table 8. Recommended Intrapartum Maternal and Neonatal Zidovudine Dosing for Prevention of Mother to Child Transmission of HIV

Maternal Intrapartum		
Zidovudine (ZDV)	**Dosing**	**Duration**
ZDV	2 mg per kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg per kg body weight per hour	Onset of labor until delivery of infant
Neonatal		
Zidovudine (ZDV)	**Dosing**	**Duration**
ZDV	**≥35 weeks gestation:** 4 mg per kg body weight per dose given orally twice daily, started as soon after birth as possible and preferably within 6-12 hours of delivery (or, if unable to tolerate oral agents, 1.5 mg per kg body weight per dose intravenously, beginning within 6–12 hours of delivery, then every 6 hours)	Birth through 6 weeks
ZDV	**<35 to ≥30 weeks gestation:** 2 mg per kg body weight per dose given orally (or 1.5 mg per kg body weight per dose intravenously), started as soon after birth as possible and preferably within 6-12 hours of delivery, then every 12 hours, advanced to every 8 hours at age 2 weeks	Birth through 6 weeks
ZDV	**<30 weeks gestation:** 2 mg per kg body weight per dose given orally (or 1.5 mg/kg/dose intravenously) started as soon after birth as possible and preferably within 6-12 hours of delivery, then every 12 hours, advanced to every 8 hours at 4 weeks of age	Birth through 6 weeks

The zidovudine dosing requirements differ for premature infants and term infants. Zidovudine is primarily cleared through hepatic glucuronidation to an inactive metabolite; this metabolic pathway is immature in neonates, leading to prolonged zidovudine half-life and clearance compared with older infants. Clearance is further prolonged in premature infants because their hepatic metabolic function is even less mature than in term infants[16-17]. The recommended zidovudine dosage for infants less than 35 weeks' gestation is 2 mg/kg body weight per dose orally every 12 hours (or 1.5 mg/kg body weight intravenously per dose every 12 hours), increasing to 2 mg/kg body weight per dose every 8 hours at age 2 weeks for infants born at 30 weeks' gestation or more or at age 4 weeks in those born at less than 30 weeks' gestation. For infants born at more than 35 weeks' gestation or greater who are unable to tolerate oral zidovudine, the drug can be given intravenously at a dose of 1.5 mg/kg body weight every 6 hours.

In the United Kingdom and many other European countries, a 4-week neonatal chemoprophylaxis regimen is recommended for infants born to mothers who have received antenatal combination ARV drug regimens[18-20]. This approach also can be considered in cases where adherence to or toxicity from the 6-week zidovudine prophylaxis regimen is a concern. In an Irish observational study, a transmission rate of 1.1% was observed in 916 infants who received 4 weeks of zidovudine infant prophylaxis following antenatal maternal combination ARV prophylaxis. That is the standard regimen in Ireland and the transmission rate was similar to that observed in the United States, where 6 weeks of infant zidovudine prophylaxis is standard[20]. A recent prospective, observational study reported that the 4-week zidovudine regimen allowed earlier recovery from anemia in otherwise healthy infants compared with the 6-week zidovudine regimen[21]. The optimal duration of neonatal zidovudine chemoprophylaxis, however, has not been established in clinical trials, and in the United States, the standard 6-week infant zidovudine regimen is recommended unless there are concerns about adherence or toxicity. Consultation with an expert in pediatric HIV infection is advised if early discontinuation of prophylaxis is considered.

Table 9. Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs in Special Circumstances Based on NICHD-HPTN 040/PACTG 1043 Regimen[1] (See Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants for further discussion.)

Maternal Intrapartum/Postpartum		
Antiretroviral (ARV) Drug	**Dosing**	**Duration**
ZDV	2 mg per kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg per kg body weight per hour	Onset of labor until delivery of infant
Neonatal (initiated as soon after delivery as possible)		
Antiretroviral (ARV) Drug	**Dosing**	**Duration**
2-drug regimen: ZDV + NVP	• ZDV: 4 mg/kg given orally twice daily[a, b] • NVP: *Birth weight 1.5–2 kg:* 8 mg per dose given orally *Birth weight >2 kg:* 12 mg per dose given orally	Birth through 6 weeks 3 doses in the first week of life • 1st dose within 48 hrs of birth (birth–48 hrs) • 2nd dose 48 hrs after 1st • 3rd dose 96 hrs after 2nd

Key to Abbreviations: 3TC = lamivudine; NFV= nelfinavir; NVP = nevirapine; ZDV = zidovudine

[1] Dosing for the 3 drug regimen is not shown because nelfinavir powder is no longer commercially available in the United States, and the 2-drug regimen is preferred.

[a] NICHD-HPTN 040/PACTG 1043 used ZDV 12 mg given orally twice daily if the birth weight was >2 kg and 8 mg given orally twice daily if the birth weight was 1.5–2.0 kg.

[b] ZDV dosing regimen is for infants ≥35 weeks' gestation. See Table 8 for recommended doses for premature infants.

General Considerations for Choice of Infant Prophylaxis

Infants born to mothers who have received standard antepartum and intrapartum ARV prophylaxis and have undetectable viral loads are at very low risk of HIV transmission. However, the risk of transmission is increased when maternal viral load at delivery is high or maternal antepartum and/or intrapartum prophylaxis was not received. Most experts feel that the potential benefit of combining zidovudine infant prophylaxis with additional ARV drugs may exceed the risk of multiple drug exposure to infants born to:

a. mothers who received antepartum and intrapartum ARV drugs but who had suboptimal viral suppression at delivery, particularly if delivery was vaginal;
b. mothers who received only intrapartum ARV drugs;
c. mothers who received no antepartum or intrapartum ARV drugs; and
d. mothers with known ARV drug-resistant virus.

In each of these situations, there is a spectrum of transmission risk that depends on a number of maternal and infant factors, including maternal viral load, mode of delivery, and gestational age at delivery. The risks and benefits of infant exposure to ARV drugs in addition to zidovudine will differ depending on where the mother/child falls in the risk spectrum. For example, an infant delivered vaginally to a mother with an HIV RNA level ≥100,000 copies/mL at delivery has a higher risk of acquiring HIV infection than an infant born by cesarean delivery to a mother with an HIV RNA level of approximately 10,000 copies/mL at delivery. Thus, a generic recommendation cannot be made regarding use of combination

drug regimens for infant prophylaxis and each situation needs to be considered individually, balancing potential benefits (in terms of preventing perinatal transmission of HIV) with risks (in terms of toxicity to the infant). In addition, appropriate drug formulations and dosing regimens for neonates are incompletely defined and data are minimal on the safety of combination drugs in the neonate (see Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis and the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection). Thus, decisions about use of combination ARV prophylaxis in infants should be made in consultation with a pediatric HIV specialist before delivery and should be accompanied by a discussion with the mothers about potential risks and benefits of this approach.

Use of combination ARV prophylaxis for infants in high-risk situations is increasing. Surveillance of obstetric and pediatric HIV infection in the United Kingdom and Ireland through the National Study of HIV in Pregnancy and Childhood noted that between 2001 and 2004, 9% of HIV-exposed infants received triple-drug prophylaxis compared with 13% between 2005 and 2008[22]. Similarly, in a Web-based poll of 134 U.S.-based perinatal HIV service providers, 62% reported using combination postnatal prophylaxis in high-risk situations in the past year. Zidovudine, lamivudine, and nevirapine was the combination regimen used most often[23].

Despite widespread use of combination ARV prophylaxis, until recently there were no data evaluating the efficacy of these regimens versus zidovudine alone in the setting of high risk of mother-to-child transmission of HIV. Results from a Phase III randomized trial in 4 countries (including the United States) were presented at the 2011 Conference on Retroviruses and Opportunistic Infections (NICHD-HPTN 040/PACTG 1043)[14]. This study enrolled 1,746 infants born to HIV-infected women who did not receive any ARV drugs during pregnancy and, hence, were at high risk of infection. The study compared infant prophylaxis with the standard 6-week zidovudine regimen and 2 different combination regimens for prevention of intrapartum transmission of HIV: 6 weeks of zidovudine plus 3 doses of nevirapine given during the first week of life (first dose at birth–48 hours; second dose 48 hours after first dose; and third dose 96 hours after second dose) and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. The risk of intrapartum transmission was significantly lower, compared with 6 weeks of zidovudine alone, in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for zidovudine alone; $P = 0.046$ for each experimental arm vs. zidovudine alone). The overall transmission rate of HIV (*in utero* + intrapartum) was also significantly lower in the 2- and 3-drug arms compared with zidovudine alone (7.1%, 7.4%, and 11.1%, respectively, $P = 0.035$ for comparison of each experimental arm with zidovudine alone)[14]. Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the 3-drug regimen than with the 2-drug or zidovudine-alone regimen (27.5% vs. 15%, $P < 0.0001$). In other studies, significantly higher rates of neutropenia and anemia have been reported with coadministration of zidovudine and lamivudine to infants[24].

The NICHD-HPTN 040/PACTG 1043 study provides proof of principle that use of a combination drug regimen for infants is more effective than zidovudine alone in the high-risk setting of no maternal antepartum administration of ARV drugs. The two-drug regimen is less complex and had lower rates of toxicity than the three-drug regimen; additionally, nelfinavir powder is no longer commercially available in the United States, is not a preferred ARV drug for pediatric treatment, and drug levels in neonates are highly variable[25]. Therefore, the two-drug regimen is recommended for prophylaxis in infants born to mothers who have not received antepartum ARV drugs.

Beyond the scenario studied in NICHD-HPTN 040/PACTG 1043, the choice of ARV drug regimens for neonates is limited (see Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis). Neonatal dosing information is not available for any of the currently available boosted protease inhibitors (PIs). In addition, use of lopinavir/ritonavir in neonates has been associated with severe and

sometimes fatal cardiac, renal, central nervous system (CNS), and metabolic toxicity[26]. Because of the potential for toxicity, lopinavir/ritonavir should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

The National Perinatal HIV Hotline (1-888-448-8765)

The National Perinatal HIV Hotline is a federally funded service providing free clinical consultation to providers caring for HIV-infected pregnant women and their infants.

Recommendations for Infant Antiretroviral Prophylaxis in Specific Clinical Situations

Infants Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression

The risk of HIV acquisition is small in infants born to women who received standard ARV prophylaxis regimens during pregnancy and labor and had undetectable viral loads at delivery or born by scheduled cesarean section to mothers with low viral loads at delivery. For example, in PACTG 316, the infection rate in infants born to women receiving antepartum PI-based therapy was 0.7% in 269 infants with HIV RNA levels of less than 400 copies/mL at delivery[2]. Such infants should receive the 6-week zidovudine infant prophylaxis regimen. In that situation, combining zidovudine with additional ARV drugs to reduce transmission risk is not recommended because the benefit would be very limited.

Infants Born to Mothers Who Have Received Antepartum/Intrapartum Antiretroviral Drugs But Have Suboptimal Viral Suppression Near Delivery

The risk of perinatal transmission is related to maternal antepartum viral load in women on no ARV drugs as well as women receiving ARVs[27-29]. Scheduled cesarean delivery is recommended for prevention of perinatal transmission in women who have received antepartum ARV drugs but have detectable viremia (HIV RNA >1,000 copies/mL) near the time of delivery (see Intrapartum Care and Transmission and Mode of Delivery). In PACTG 316, transmission occurred in 0% of 17 infants when maternal HIV RNA levels at delivery were >10,000 copies/mL and delivery was by scheduled cesarean delivery[2]. However, not all women with detectable viremia near delivery will undergo cesarean delivery. The risk of acquisition of HIV will be higher in infants born to mothers with higher viral loads near delivery, particularly if delivery is vaginal. The gradient of transmission risk is based on HIV RNA levels. In the Women and Infants Transmission Study (WITS), the risk of transmission of HIV was ≤1.8% in women who received triple-combination ARV prophylaxis and had HIV RNA levels <30,000 copies/mL at delivery; it increased to 4.8% in women with HIV RNA levels ≥30,000 copies/mL[29].

All infants should receive zidovudine for 6 weeks. No specific data address whether a more intensive combination infant prophylaxis regimen (two or three drugs) provides additional protection against transmission when maternal antepartum/intrapartum prophylaxis is received but viral replication near delivery is significant. Elective cesarean section is recommended for pregnant women with HIV RNA levels >1,000 copies/mL near delivery. Extrapolation of findings from the previously discussed NICHD-HPTN 040/PACTG 1043 study[14] suggests that combination infant prophylaxis can be considered, depending on assessment of risk based on maternal viral load and mode of delivery. That decision should be made in consultation with a pediatric HIV specialist before delivery and accompanied by maternal counseling on the potential risks and benefits of this approach.

Infants Born to Mothers Who Received Only Intrapartum Antiretroviral Drugs

All infants whose mothers have received only intrapartum ARV drugs should be given zidovudine for 6

weeks. This infant prophylaxis regimen is a critical component of prevention when no maternal antepartum ARV drugs have been received. The PETRA study demonstrated that intrapartum prophylaxis alone, without infant prophylaxis, is ineffective in reducing perinatal transmission[3]. A study in Thailand indicated that longer infant prophylaxis with zidovudine (6 weeks vs. 3 days) is required for optimal efficacy when maternal antenatal exposure to zidovudine is <4 weeks[30].

Infant prophylaxis with zidovudine should be initiated as soon after delivery as possible. In the NICHD-HPTN 040/PACTG 043 trial previously discussed, 41% of women received zidovudine during labor. Administration of intrapartum zidovudine did not affect transmission rates. The results of this study support use of a two-drug regimen, involving 6 weeks of zidovudine plus three doses of nevirapine in the first week of life, because combination regimens were found to have increased efficacy in reducing intrapartum transmission compared with use of zidovudine alone and the three-drug regimen was associated with increased toxicity and nelfinavir powder is no longer commercially available in the United States[14].

Infants Born to Mothers Who Did Not Receive Antepartum or Intrapartum Antiretroviral Drugs

Infants of HIV-infected mothers who have received neither antepartum nor intrapartum ARV drugs should be started on ARV prophylaxis as soon after delivery as possible. Observational and Phase III randomized studies suggest that prophylaxis provided to infants alone may be helpful in preventing transmission of HIV. Epidemiologic data from a New York State study indicated a decline in transmission when infants were given zidovudine for the first 6 weeks of life compared with no prophylaxis[31]. Transmission rates were 9% (95% confidence interval [CI], 4.1%–17.5%) with zidovudine-alone prophylaxis in newborns (initiated within 48 hours after birth) versus 27% (95% CI, 21%–33%) with no zidovudine prophylaxis. For most infants in this study, prophylaxis was initiated within 12 hours of birth[32].

The two-drug regimen of 6 weeks of zidovudine plus three doses of nevirapine in the first week of life is recommended based on the results of the NICHD-HPTN 040/PACTG 1043 study, which demonstrated increased efficacy of combination regimens in reducing intrapartum transmission compared with use of zidovudine alone in infants[14]. Prophylaxis should be initiated as soon after delivery as possible.

The interval during which infant prophylaxis can be initiated and still be of benefit is undefined. In the New York State study, when prophylaxis was delayed beyond 48 hours after birth, no efficacy could be demonstrated. Data from animal studies indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, ARV prophylaxis initiated 24–36 hours after exposure usually has been ineffective in preventing infection, although a delay in administration has been associated with decreased viremia[33-35]. In the NICHD-HPTN 040/PACTG 1043 study, infant regimens were initiated within 48 hours of life and usually within 12 hours of life[14]. Initiation of infant prophylaxis after age 2 days is not likely to be efficacious in preventing transmission and, by age 14 days, infection already would be established in most infants[36]. Initiating prophylaxis as soon after delivery as possible increases its potential efficacy and minimizes potential harm, such as development of resistant virus, if infection has occurred.

Infants Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal prophylactic regimen for newborns delivered by women with ARV drug-resistant virus is unknown. ARV prophylaxis for infants born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery.

Data from the WITS suggest that in women who have mixed zidovudine-resistant and -sensitive viral populations, the zidovudine-sensitive rather than -resistant virus may be preferentially transmitted[37-38].

Thus, the 6-week infant zidovudine prophylaxis (along with maternal intravenous intrapartum zidovudine prophylaxis) continues to be recommended, even when maternal zidovudine-resistant virus with thymidine-associated mutations (TAMs) is identified.

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility[38]. However, transmission from mother to child of multidrug-resistant virus has been reported[39-41].

For these newborns, use of zidovudine in combination with other ARV drugs, selected on the basis of maternal virus resistance testing, can be considered. The efficacy of this approach for prevention of transmission, however, has not been proven in clinical trials, and for many drugs, appropriate dosing regimens for neonates are incompletely defined. Decisions regarding use of additional drugs should be made in consultation with a pediatric HIV specialist and will depend on maternal history of past and current ARV drug exposure, HIV RNA levels at or near delivery, current and previous maternal resistance testing, and availability of drug formulation and dosing information in the infant. ARV drugs with pharmacokinetic (PK) and safety data in neonates sufficient to support their addition to zidovudine include lamivudine and nevirapine; although there are pharmacokinetic data in neonates for nelfinavir, nelfinavir powder for oral use is no longer commercially available in the United States.

Breastfeeding Infants of Mothers Diagnosed with HIV Infection Postpartum

Breastfeeding should be stopped until infection is confirmed or ruled out in women who are breastfeeding at the time of HIV diagnosis or suspected to be HIV infected. Pumping and temporarily discarding breast milk can be recommended to mothers who are suspected of being HIV infected but whose infection is not yet confirmed and who want to continue to breastfeed. If HIV infection is ruled out, breastfeeding can resume.

The risk of acquisition of HIV associated with breastfeeding depends on multiple infant and maternal factors, including maternal viral load and CD4 cell count[42]. Infants of women who develop acute HIV infection while breastfeeding are at greater risk of becoming infected than are those of women with chronic HIV infection[43] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count[44].

Other than discontinuing breastfeeding, optimal strategies for managing infants born to HIV-infected mothers who breastfed their infants prior to HIV diagnosis have yet to be defined. Some experts would consider the use of post-exposure prophylaxis in infants for 4–6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance compared with other nonoccupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than in a single exposure[45].

Several studies of infants breastfed by women with chronic HIV infection have shown that daily infant nevirapine or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding[8, 46-47]. The NICHD-HPTN 040/PACTG 043 study demonstrated that combination ARV prophylaxis was more effective than zidovudine prophylaxis alone for preventing intrapartum transmission in mothers who have not received antepartum ARV drugs[14]. However, whether the combination regimens in this trial are effective for preventing transmission after cessation of breastfeeding in mothers with acute HIV infection is unknown.

An alternative approach favored by some experts would be to offer a combination ARV regimen that would be effective for treatment of HIV, should the infant become infected. If this route is chosen, current recommendations for treatment should guide selection of an appropriate combination ARV regimen

(see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection). Regardless of whether post-exposure prophylaxis or "preemptive therapy" is chosen, the duration of the intervention is unknown. A 28-day course seems reasonable based on current recommendations for nonoccupational HIV exposure[45]. As in other situations, decisions regarding administration of a prophylactic or preemptive treatment regimen should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach.

Infants should be tested for HIV infection at baseline and 4–6 weeks, 3 months, and 6 months after recognition of maternal infection to determine whether they are HIV infected. In infants younger than age 18 months, HIV DNA or RNA polymerase chain reaction (PCR) tests should be used for diagnosis. HIV DNA PCR is preferable for infants who are receiving combination ARV prophylaxis or preemptive treatment. HIV antibody assays can be used in infants older than age 18 months. Post-exposure ARV prophylaxis or preemptive treatment should be discontinued in infants who are found to be HIV infected while receiving one of these regimens. Resistance testing then should be performed and an appropriate combination therapy regimen initiated (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection).

Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis

Infant prophylaxis with zidovudine has been associated with only minimal toxicity, consisting primarily of transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see Initial Postnatal Management). Data are limited on the toxicity to infants of exposure to multiple ARV drugs.

The latest information on neonatal dosing for ARV drugs can be found in the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Other than zidovudine, lamivudine is the nucleoside reverse transcriptase inhibitor (NRTI) with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1 week[3, 14, 48]. Six weeks of infant zidovudine/lamivudine exposure also has been reported; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the infants also had *in utero* exposure to maternal combination therapy.

In a French study, more severe anemia and neutropenia were observed in infants exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort exposed only to maternal and infant zidovudine. Anemia was reported in 15% and neutropenia in 18% of infants exposed to zidovudine/lamivudine, with 2% of infants requiring blood transfusion and 4% requiring treatment discontinuation for toxicity[24]. Similarly, in a Brazilian study of maternal antepartum and 6-week infant zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of infants[49]. In a Phase I study of stavudine in pregnant women, infants received 6 weeks of zidovudine/lamivudine and a single dose of stavudine at ages 1 and 6 weeks; 6 of 14 (43%) infants experienced Grade 3 hematologic toxicity after birth (36% neutropenia and 7% anemia)[50]. Finally, in three Phase I studies of PIs (saquinavir/ritonavir, indinavir, or nelfinavir) in pregnancy, a total of 52 infants received 6 weeks of zidovudine/lamivudine (in 26 infants, zidovudine/lamivudine was combined with nelfinavir); Grade 2 or higher hematologic toxicity was observed in 46%–62% of infants[51-53]. In the NICHD-HPTN 040/PACTG 1043 study, significantly higher rates of Grade 3 or 4 neutropenia were seen with a three-drug regimen including zidovudine and lamivudine than with zidovudine alone or a two-drug regimen with zidovudine and nevirapine (27.5% vs. 16% and 15%, respectively, $P < 0.0001$)[14]. In contrast, Grade 3 or 4 anemia occurred in 23%–27% of infants, with no differences between study arms[14].

Experience with other NRTI drugs for neonatal prophylaxis is more limited[54-55]. Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs[24, 56-59].

Nevirapine is the only non-nucleoside reverse transcriptase inhibitor (NNRTI) drug with a pediatric drug formulation and neonatal dosing information (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection)[60]. In rare cases, chronic multiple-dose nevirapine has been associated with severe and potentially life-threatening rash and hepatic toxicity. These toxicities have not been observed in infants receiving single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding infants receiving nevirapine prophylaxis daily for 6 weeks to 6 months to prevent transmission of HIV via breast milk[8, 14, 46-47, 61]. Resistance to nevirapine can occur, however, with exposure to nevirapine in infants who become infected despite prophylaxis[62-63]. ARV drug-resistance testing is recommended for all HIV-infected infants before initiation of ART (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection).

Of the PIs, nelfinavir, lopinavir/ritonavir, ritonavir, tipranavir, and fosamprenavir have pediatric drug formulations. Dosing information for newborn infants is only available for nelfinavir, which has highly variable levels in neonates and for which high doses are required; however, nelfinavir powder is no longer commercially available in the United States[25, 53, 55]. PK data are available for treatment of HIV-infected infants 2–6 weeks of age with lopinavir/ritonavir. Although the lopinavir area under the curve (AUC) was significantly lower with dosing 300 mg lopinavir/75 mg ritonavir per meter^2 body surface area twice daily than observed for infants >6 weeks of age, treatment was well tolerated and 80% of 10 infants had viral control at 6 months[64]. Studies are ongoing but data are not yet available for infants <2 weeks of age. However, in 4 premature infants (2 sets of twins) started on lopinavir/ritonavir from birth, heart block developed that resolved after drug discontinuation[65-66]. In studies of adults, both ritonavir and lopinavir/ritonavir cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Based on these and other post-marketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death, predominantly in preterm neonates, the Food and Drug Administration (FDA) now recommends that lopinavir/ritonavir NOT be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

Dosing for premature infants is available for only zidovudine (see Table 8), making use of other ARV drugs in this group more problematic. In preterm infants immature renal and hepatic metabolism increases the risk of overdosing and toxicity. Because zidovudine is the only ARV drug available in an intravenous formulation, the 6-week zidovudine prophylaxis regimen is recommended for preterm infants at gestational age-appropriate doses. Use of ARV drugs other than zidovudine cannot be recommended in premature infants because data on dosing and safety are lacking.

References

1. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* Nov 3 1994;331(18):1173-1180.
2. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA.* Jul 10 2002;288(2):189-198.
3. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* Apr 6 2002;359(9313):1178-1186.
4. Taha TE, Kumwenda NI, Hoover DR, et al. Nevirapine and zidovudine at birth to reduce perinatal transmission of HIV

in an African setting: a randomized controlled trial. *JAMA.* Jul 14 2004;292(2):202-209.

5. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet.* Oct 11 2003;362(9391):1171-1177.
6. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS.* Jun 12 2006;20(9):1281-1288.
7. Gray GE, Urban M, Chersich MF, et al. A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS.* Aug 12 2005;19(12):1289-1297.
8. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med.* Jul 10 2008;359(2):119-129.
9. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers with triple antiretroviral therapy in Dar es Salaam, Tanzania: the Mitra Plus study. *J Acquir Immune Defic Syndr.* Nov 1 2009;52(3):406-416.
10. Peltier CA, Ndayisaba GF, Lepage P, et al. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. *AIDS.* Nov 27 2009;23(18):2415-2423.
11. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med.* Jun 17 2010;362(24):2282-2294.
12. de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infect Dis.* Mar 2011;11(3):171-180.
13. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis.* Mar 1 2003;187(5):725-735.
14. Nielsen-Saines K, Watts DH, Santos VV, al e. Phase III randomized trial of the safety and efficacy of three neonatal antiretroviral regimens for preventing intrapartum HIV-1 transmission (NICHD HPTN 040/PACTG 1043). *18th Conference on Retroviruses and Opportunistic Infections.* Boston, MA, 2011.
15. World Health Organization. http://www.who.int/hiv/pub/mtct/antiretroviral2010/en/index.html. 2010.
16. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* Jan 2003;142(1):47-52.
17. Mirochnick M, Capparelli E, Connor J. Pharmacokinetics of zidovudine in infants: a population analysis across studies. *Clin Pharmacol Ther.* Jul 1999;66(1):16-24.
18. de Ruiter A, Mercey D, Anderson J, et al. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med.* Aug 2008;9(7):452-502.
19. Ferguson W, Good M, Walksh A, al. e. Four weeks of neonatal antiretroviral therapy (ART) is sufficient to optimally prevent mother to child transmission (PMTCT) of HIV. *48th Annual ICAAC/IDSA 46th Annual Meeting.* Washington, DC, 2008.
20. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. *Pediatr Infect Dis J.* May 2011;30(5):408-412.
21. Lahoz R, Noguera A, Rovira N, et al. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J.* Apr 2010;29(4):376-379.
22. Haile-Selassie H, Townsend C, Tookey P. Use of neonatal post-exposure prophylaxis for prevention of mother-to-child HIV transmission in the UK and Ireland, 2001-2008. *HIV Med.* Jan 20 2011.

23. McKeegan K, Rutstein R, Lowenthal E. Postnatal infant HIV prophylaxis: a survey of U.S. practice. *AIDS Patient Care STDS.* Jan 2011;25(1):1-4.

24. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA.* Apr 25 2001;285(16):2083-2093.

25. Mirochnick M, Nielsen-Saines K, Pilotto JH, et al. Nelfinavir and lamivudine pharmacokinetics during the first two weeks of life. *Pediatr Infect Dis J.* Sep 30 2011;30(9):769-772.

26. Boxwell D, Cao K, Lewis L, Marcus K, Nikhar B. Neonatal toxicity of Kaletra oral solution: LPV, ethanol or propylene glycol? *18th Conference on Retroviruses and Opportunistic Infections.* Boston, MA, 2011.

27. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* Aug 5 1999;341(6):385-393.

28. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med.* Aug 5 1999;341(6):394-402.

29. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr.* Apr 15 2002;29(5):484-494.

30. Lallemant M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med.* Oct 5 2000;343(14):982-991.

31. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med.* Nov 12 1998;339(20):1409-1414.

32. Fiscus SA, Schoenbach VJ, Wilfert C. Short courses of zidovudine and perinatal transmission of HIV. *N Engl J Med.* Apr 1 1999;340(13):1040-1041; author reply 1042-1043.

33. Van Rompay KK, Otsyula MG, Marthas ML, Miller CJ, McChesney MB, Pedersen NC. Immediate zidovudine treatment protects simian immunodeficiency virus-infected newborn macaques against rapid onset of AIDS. *Antimicrob Agents Chemother.* Jan 1995;39(1):125-131.

34. Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. *Science.* Nov 17 1995;270(5239):1197-1199.

35. Bottiger D, Johansson NG, Samuelsson B, et al. Prevention of simian immunodeficiency virus, SIVsm, or HIV-2 infection in cynomolgus monkeys by pre- and postexposure administration of BEA-005. *AIDS.* Feb 1997;11(2):157-162.

36. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS.* Sep 1995;9(9):F7-11.

37. Colgrove RC, Pitt J, Chung PH, Welles SL, Japour AJ. Selective vertical transmission of HIV-1 antiretroviral resistance mutations. *AIDS.* Dec 3 1998;12(17):2281-2288.

38. Bauer GR, Colgrove RC, Larussa PS, Pitt J, Welles SL. Antiretroviral resistance in viral isolates from HIV-1-transmitting mothers and their infants. *AIDS.* Aug 22 2006;20(13):1707-1712.

39. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS.* Jun 10 2005;19(9):989-990.

40. Desai N, Mathur M. Selective transmission of multidrug resistant HIV to a newborn related to poor maternal adherence. *Sex Transm Infect.* Oct 2003;79(5):419-421.

41. De Jose MI, Ramos JT, Alvarez S, Jimenez JL, Munoz-Fernandez MA. Vertical transmission of HIV-1 variants resistant to reverse transcriptase and protease inhibitors. *Arch Intern Med.* Dec 10-24 2001;161(22):2738-2739.

42. Kuhn L, Reitz C, Abrams EJ. Breastfeeding and AIDS in the developing world. *Curr Opin Pediatr.* Feb 2009;21(1):83-93.

43. Van de Perre P, Lepage P, Homsy J, Dabis F. Mother-to-infant transmission of human immunodeficiency virus by breast milk: presumed innocent or presumed guilty? *Clin Infect Dis.* Sep 1992;15(3):502-507.

44. Daar ES. Virology and immunology of acute HIV type 1 infection. *AIDS Res Hum Retroviruses.* Oct 1998;14 Suppl 3:S229-234.

45. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. *MMWR Recomm Rep.* Jan 21 2005;54(RR-2):1-20.

46. Six Week Extended-Dose Nevirapine (SWEN) Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet.* Jul 26 2008;372(9635):300-313.

47. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med.* Jun 17 2010;362(24):2271-2281.

48. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis.* Nov 1998;178(5):1327-1333.

49. Lambert JS, Nogueira SA, Abreu T, et al. A pilot study to evaluate the safety and feasibility of the administration of AZT/3TC fixed dose combination to HIV infected pregnant women and their infants in Rio de Janeiro, Brazil. *Sex Transm Infect.* Dec 2003;79(6):448-452.

50. Wade NA, Unadkat JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis.* Dec 15 2004;190(12):2167-2174.

51. Zorrilla CD, Van Dyke R, Bardeguez A, et al. Clinical response and tolerability to and safety of saquinavir with low-dose ritonavir in human immunodeficiency virus type 1-infected mothers and their infants. *Antimicrob Agents Chemother.* Jun 2007;51(6):2208-2210.

52. Unadkat JD, Wara DW, Hughes MD, et al. Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother.* Feb 2007;51(2):783-786.

53. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr.* Jun 1 2005;39(2):189-194.

54. Gray G, Violari A, McIntyre J, et al. Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: its role in preventing HIV infection in infants. *J Acquir Immune Defic Syndr.* Jun 2006;42(2):169-176.

55. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, et al. Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr.* Apr 15 2002;29(5):455-463.

56. Torres SM, Walker DM, Carter MM, et al. Mutagenicity of zidovudine, lamivudine, and abacavir following in vitro exposure of human lymphoblastoid cells or in utero exposure of CD-1 mice to single agents or drug combinations. *Environ Mol Mutagen.* Apr-May 2007;48(3-4):224-238.

57. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, Blanche S. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS.* Sep 26 2003;17(14):2053-2061.

58. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis.* Oct 15 2006;194(8):1089-1097.

59. Feiterna-Sperling C, Weizsaecker K, Buhrer C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr.* May 1 2007;45(1):43-51.

60. Mirochnick M, Nielsen-Saines K, Pilotto JH, et al. Nevirapine concentrations in newborns receiving an extended prophylactic regimen. *J Acquir Immune Defic Syndr.* Mar 1 2008;47(3):334-337.

61. Coovadia H, Brown E, Maldonado Y, al. e. Efficacy of Extended Daily Infant Nevirapine (NVP) through Age 6 Months Compared to 6 Weeks for Prevention of Postnatal Mother-to-Child Transmission (MTCT) of HIV through Breastfeeding (BF). *18th Conference on Retroviruses and Opportunistic Infections.* Boston, MA, 2011.

62. Moorthy A, Gupta A, Bhosale R, et al. Nevirapine resistance and breast-milk HIV transmission: effects of single and extended-dose nevirapine prophylaxis in subtype C HIV-infected infants. *PLoS One.* 2009;4(1):e4096.

63. Fogel J, Hoover DR, Sun J, et al. Analysis of nevirapine resistance in HIV-infected infants who received extended nevirapine or nevirapine/zidovudine prophylaxis. *AIDS.* Apr 24 2011;25(7):911-917.

64. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J.* Mar 2009;28(3):215-219.

65. Lopriore E, Rozendaal L, Gelinck LB, Bokenkamp R, Boelen CC, Walther FJ. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* Nov 30 2007;21(18):2564-2565.

66. McArthur MA, Kalu SU, Foulks AR, Aly AM, Jain SK, Patel JA. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* Dec 2009;28(12):1127-1129